REMARKS

Response to §112 Enablement Rejection

In the outstanding Office Action, the Examiner rejected pending claims 1-4, 13, and 17-19 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement, asserting that the instant specification fails to provide any guidance on the amount of creatine compound to be used for stimulating the hair growth or increasing DNA synthesis, that the instant specification fails to provide evidence supporting efficacy of compounds other than creatine in stimulating the hair growth or increasing DNA synthesis, that further testing would be necessary to use the claimed invention, and that the practice of the full scope of the invention would therefore require undue experimentation.

Applicants respectfully disagree with the Examiner and hereby provide point-by-point rebuttals of the Examiner's assertions:

(1) The Amount of Creatine Compound to be Used

In the outstanding Office Action, the Examiner asserted that "*[s]pecification under paragraph 21 admits that certain concentration is effective in growing dermalpapilla cells,*" that "*[c]laim 1 does not recite any concentration,*" and at "*[t]his value can be any molar concentration,*" and that "*[t]he instant specification gives one skilled in the art no indication that the one could use any amount of creatine [compound] ... and increase DNA synthesis and stimulate hair growth in hair plugs and have a reasonable expectation of success*" (see the outstanding Office Action, page 3, lines 15-16; page 5, lines 5-6 and 21-22; and page 6, lines 1-2).

However, it is never Applicants' intent that the claimed invention of the present application should cover any amount or any concentration of creatine compound, as Examiner

asserted. On the contrary, claims 1 and 13 of the present application, from which claims 2-4 and 17-19 depend, both recite **"a follicle-stimulating effective amount"** of creatine compound, which clearly and unequivocally imposes a limitation on the amount of creatine compound that can be used in the claimed invention for increasing DNA synthesis of dermal papilla cells or stimulating hair growth in hair plugs. The instant specification defines the term "follicle-stimulating effective amount" as the **"amount that is capable of increasing the hair growth of a follicle at 20% above the growth observed in an untreated follicle"** (see the instant specification, page 3, lines 20-23).

It is well established that a specification disclosure that requires a person of ordinary skill in the art to make certain adjustments or experiments to make and use the claimed invention can still satisfy the enablement requirement of 35 U.S.C. $112, first paragraph, as long as the amount and kind of experimentation required is reasonable and is not "undue." For example, the Federal Circuit Court (hereinafter "the Court") ruled in *Cross* v. Iizuka, 224 USPQ 739 (Fed. Cir. 1985) that the enablement requirement of 35 U.S.C. §112, first paragraph was met, even though the specification in issue did not disclose the dosage levels for the claimed compounds *per se*. The Court stated that because one skilled in the art could determine the dosage level by using a microsome assay that was known to those skilled in the art without inventive skill or undue experimentation, the how-to-use aspect of the §112 enablement requirement was satisfied. Id., at 748. Further, the requirement for a considerable amount of experimentation is permissible under 35 U.S.C. $112, first paragraph, if such experimentation is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the present case, Example 2 of the instant specification describes, in step-by-step detail, an essay for measuring the increase of hair growth in hair plugs, i.e., follicles, above the growth observed in untreated hair plugs (see the instant specification, pages 9-11). Although the instant specification only tested creatine at 1mM to prove that at such concentration creatine was capable of increasing the hair growth of follicles by 75%+ above the growth observed in untreated hair follicles (see Table 5 on page 11 of the instant specification), a person ordinarily skilled in the art can readily repeat the essay described in Example 2 of the instant specification to test the efficacy of creatine at other concentrations in increasing the hair growth of follicles or to screen other creatine compounds and determine the corresponding "follicle-stimulating effective amount" for such other creatine compounds. In other words, by simply repeating the essay described in Example 2 of the instant specification, one ordinarily skilled in the art can readily determine whether or not a specific concentration of a specific creatine compound constitute the "follicle-stimulating effective amount" within the meaning of claims 1-4, 13 and 17-19 of the present application, i.e., whether or not such specific concentration of the specific creatine compound can increase the hair growth of follicles by at least 20% above the growth observed in untreated follicles. Such repetition of a well-described essay does not involve any inventive skill; nor does it constitute "undue" experimentation. Instead, it is merely routine experimentation for which the instant specification has already provided detailed, step-by-step instruction.

Therefore, Applicants submit that the description in the instant specification complies with the enablement requirement under 35 U.S.C. §112, first paragraph with respect to the "follicle-stimulating effective amount" recited by claims 1-4, 13 and 17-19 of the present application.

(2) The Creatine Compound to be Used

In the outstanding Office Action, the Examiner asserted that the creatine compound as recited by the pending claims of the present application *"can be any derivative [of] creatine,"* that *"[t]here is no structural similarity between creatine and cyclocreatine,"* and that *"the [testing] results are with respect to creatine and not its metabolite creatinephosphate or cyclocreatine"* (see the Office Action, page 5, lines 8-11).

However, it is never Applicants' intent that the claimed invention of the present application should cover any type of creatine derivatives or analogues, as Examiner asserted. On the contrary, the instant specification specifically defines the term **"creatine compound(s)"** as **"creatine and creatine analogues that exhibit the same type of stimulatory activity"** (see the instant specification, page 3, lines 19-20), which clearly and unequivocally imposes a limitation on the type of creatine derivatives or analogues that can be used in the claimed invention, i.e., such creatine derivatives or analogues have to exhibit follicle-stimulating activity.

It is well known that creatine phosphate can be readily converted *in vivo* to and from creatine by an enzyme called creatine kinase, which is present in all vertebrates (see attached information for "Creatine" downloaded from http://en.wikipedia.orglwiki/Creatine on October 8). Therefore, creatine phosphate, when applied to human skin or skin cells, can be readily converted *in vivo* to creatine to stimulate the hair growth in follicles. Therefore, it is certain that creatine phosphate will exhibit the same type of stimulatory activity as creatine.

Although cyclocreatine is structurally different from creatine, it has been well accepted as a functional analogue of creatine. Specifically, both creatine and cyclocreatine are substrates for mitochondrial creatine kinase, and cyclocreatine has been recognized as the most kinetically active analog of creatine in the creatine kinase reaction (see Matthews et al., "Neuroprotective

Effects of Creatine and Cyclocreatine in Animal Models of Huntington's Disease," THE JOURNAL OF NEUROSCIENCE, January 1, 1998, 18(1):156-163). Therefore, it is highly likely that cyclocreatine will exhibit the same type of stimulatory activity as creatine.

Further, it has been well established that the mere presence of certain inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled, as long as one skilled in the art could readily determine which embodiments would be inoperative or operative with reasonable experimentation. Atlas Powder Co. v. E.I. *du* Pont de *Nemours &* Co., 224 USPQ 409,414 (Fed. Cir. 1984).

In the present case, even if assuming arguendo that cyclocreatine or some other known functional analogue of creatine was not effective in stimulating the hair growth in follicles, the enablement requirements under 35 U.S.C. §112, first paragraph can still be met, because one ordinarily skilled in the art can readily follow the essay described in step-by-step detail by Example 2 of the instant specification to determine whether cyclocreatine or the other functional analogue of creatine constitutes the "creatine compound" within the meaning of claims 1-4, 13 and 17-19 of the present application, i.e., whether cyclocreatine or the other functional analogue of creatine is effective in stimulating hair growth in follicles or not. As mentioned hereinabove, such repetition of a well-described essay does not involve any inventive skill or constitute "undue" experimentation. Instead, it is merely routine experimentation for which the instant specification has already provided detailed, step-by-step instruction.

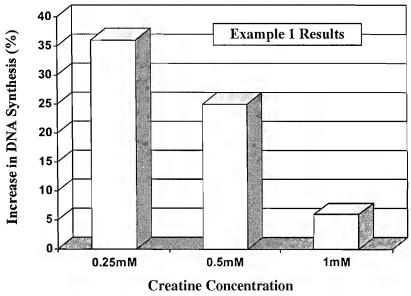
Therefore, Applicants submit that the description in the instant specification complies with the enablement requirement under 35 U.S.C. §112, first paragraph with respect to the "creatine compound" recited by claims 1-4, 13 and 17-19 of the present application.

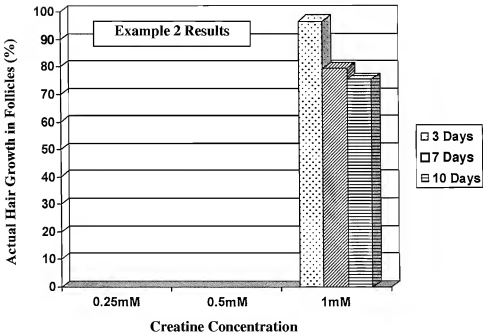
(3) Correlation between DNA Synthesis Test and Hair Growth Stimulation Test

In the outstanding Office Action, the Examiner asserted that "[t]here is no correlation between the test results for DNA synthesis and stimulating hair growth in hair plugs," because the test results in Examples 1 and 2 of the instant specification show that at 1mM, creatine only increased the DNA synthesis by 6% but increased hair growth in hair plugs by 75%+.

Applicants respectfully disagree with the Examiner's interpretation of the test results, for the following reasons:

Example 1 of the instant specification tested the effectiveness of creatine in increasing DNA synthesis in dermal papilla cells at three (3) different concentrations, i.e., 0.25mM, 0.5mM, and 1mM. Although creatine was capable of increasing DNA synthesis at all 3 concentrations, it was discovered that creatine at relatively lower concentration, i.e., 0.25mM, was more effective in increasing DNA synthesis than at relatively high concentration, i.e., 1mM. Example 2 of the instant specification continued to test the effectiveness of creatine at only one (1) concentration, i.e., the relatively high concentration of 1mM, in stimulating hair growth in follicles, and discovered that such relatively high concentration of creatine was effective in stimulating the hair growth by 75%+. The test results of Examples 1 and 2 can be graphically represented as follows:





Such test results from Examples 1 and 2 do not contradict with each other in any way. On one hand, Example 1 establishes the dose-dependency of creatine in increasing DNA synthesis and shows that relatively low concentration of creatine has a stronger stimulatory effect for DNA synthesis. On the other hand, Example 2 proves that the increase in DNA synthesis can be translated into actual increase in hair growth and shows that 1mM of creatine, although only increasing DNA synthesis by 6%, can nevertheless increase the hair growth by 75%+. In other words, Example 2 was carried out to prove that a relatively small increase in DNA synthesis can nevertheless be translated into a significant increase in hair growth. Based on the test results provided by Examples 1 and 2 of the instant specification, a person ordinarily skilled in the art can readily predict that when used at relatively lower concentrations, i.e., 0.25mM or 0.5mM, creatine can result in even more significant increase in hair growth, such as, for example, >100%.

Therefore, Applicants submit that the test results from Examples 1 and 2 not only do not contradict with each other, despite the Examiner's assertion in the outstanding Office Action.

Based on the foregoing, Applicants respectfully submit that claims 1-4, 13, and 17-19 of the present application are in compliance with the enablement requirements of 35 U.S.C. §112, first paragraph, and the Examiner is hereby requested to reconsider, and upon reconsideration to withdraw, the §112 rejection against claims 1-4, 13, and 17-19 of the present application.

New Claims *25* and 26

Although Applicants are not willing to limit the scope of the present application to the specific type of compound and specific concentrations tested in the examples of the instant specification, new claims 25 and 26 are added herein, which recite only creatine at a concentration ranging from about 0.25 mM to about 1mM, in order to expedite the proceeding in the present case.

Respectfully submitted,

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